BENHA MEDICAL JOURNAL bmj
Print ISSN 1110-208X.
Online ISSN 2357-0016
25

Assessment of OCTA and Multifocal Electroretinogram in Eyes with and Without Diabetic Retinopathy

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Received: 15 October 2024

Accepted:4 January 2025

Abstract:

Background: Diabetic retinopathy (DR) is a highly prevalent complication for DM patients. It may be a leading cause of visual impairment among vital groups of population. This study aimed to assess the retinal structure and function using Optical coherence tomography angiography (OCTA) and multifocal electroretinogram (mfERG), respectively, in eyes with and without DR and interrelationship between retinal structure and function. **Methods:** This prospective study included 60 eyes of 60 patients who undergone assessment of OCTA and mfERG. Patients were divided into 3 equal groups: Group 1: healthy individuals without diabetes mellitus, Group 2: diabetic patients without DR, and Group 3: diabetic patients with DR." Group 3: diabetic patients with DR. **Results:** In diabetic patients without retinopathy, we found a good positive correlation between Cub Avg. thickness and mfERG in Ring 2 Resp den. FAZ area and Ring 5 Resp den. FAZ perimeter and Ring 4 Resp den, and Ring 5 Resp den. and A good negative correlation between Cub Avg. thickness and Ring 5 p1. implicit time, while in patients with retinopathy we found a good positive correlation with Ring 1 Resp den, Ring 5 p1. implicit time and FAZ area. **Conclusion:** both OCTA and mfERG are beneficial to early detect diabetic macular changes and can detect morphological and functional retinal changes related to diabetes. Both vascular and functional impairment assessed by OCTA and mfERG respectively and their parameters become more severe by increasing the severity and progression of DR.

Keywords: OCTA; Multifocal Electroretinogram; Eyes; Diabetic Retinopathy.

Introduction

Diabetic retinopathy (DR) is a highly prevalent complication for DM patients. It affects almost one-third of DM patients and may be a leading cause of visual impairment among vital groups of population [(1)]. DR is a micro-angiopathy affecting the retinal pre- capillaries arterioles, capillaries and venules. Retinopathy has features of both micro-vascular occlusion and leakage. There is an asymptomatic stage from developing DM to the appearance of clinical signs of DR in which clinically unnoticed microvascular changes and neural retinal damage occur and progress [(2)].

The previous evidence from published studies proposed that clinical vascular changes follow the neural changes occurring in the retina of those cases [(3)]**.** Hence, several methods have been introduced to assess local retinal function in DM, and among them; studies have shown that multifocal electroretinogram (mfERG) may be a highly sensitive tool for detecting early neural dysfunction in the retina. Moreover, mfERG revealed that the implicit time increased significantly in the eyes of DM patients without DR compared to controls [(4)].

A study that generated a model using the abnormal mfERG for patients without DR and other risk factors demonstrated that mfERG can predict the beginning of DR in patients with DM [(5)]. Hence, mfERG implicit time and amplitude may be considered as good predictors of DR in retinas with no retinopathy which can be a valid tool for clinicians and researchers with follow-up either through more tight diabetic control and trial of novel therapies that can delay or even prevent the progression of DR [(6)].

Optical coherence tomography angiography (OCTA) defined retinal vascular and choriocapillaris parameters in diabetic patients without clinically evident DR. Hence, OCTA can detect microvascular changes that are not otherwise noted on clinical examination. These pre-clinical findings may facilitate earlier intervention for improved glycemic control and prevention of the onset of clinical retinopathy. However, neural dysfunction that is detected by mfERG precedes preclinical vascular changes that can be detected by OCTA which allows earlier intervention to protect the patients [(7)].

The purpose of this study was to assess to assess the retinal structure and function using OCTA and mfERG, respectively, in eyes with and without DR and interrelationship between retinal structure (OCTA) and function (mfERG) respectively.

Subjects and methods

This prospective clinical study included 60 eyes of 60 patients who undergone assessment of OCTA and mfERG. The study was carried out at Ophthalmic Department, Faculty of Medicine, Benha University during the period from December 2022 to January 2024.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

Inclusion criteria were adult with age more than 18 years, both sexes, patients with type 1 or 2 diabetes for a period more than 5 years, patients had intact clear cornea and intact anterior chamber and cooperated individuals that can-do informed consent.

Exclusion criteria were high error of refraction ≥ +4 D and ≥ - 6 D, poorly controlled hypertension, patients with corneal diseases, any media opacities obscuring retinal imaging, with symblepharon or conjunctival scar, with previous intraocular or ocular surface surgery, with posterior segment diseases other than DR, with autoimmune disease, underlying systemic diseases, ACE inhibitors and ARBs, severely impaired liver and kidney function parameters,

patients with end organ damage, with neuropathies and pregnant or breastfed females.

Grouping:

Participants were selected and divided into 3 equal groups: Group 1: (n=20, include 20 eyes) included healthy individuals without diabetes mellitus representing the control group. Group 2: (n=20, include 20 eyes) diabetic patients without DR, and Group 3: (n=20, include 20 eyes) diabetic patients with DR, including 10 eyes with NPDR and 10 eyes with PDR."

All studied cases were subjected to the following: History including [Personal history (age, sex, family history, residence and occupation), present history (history of onset, duration and progression of diabetes, type of diabetes, patients first complaint, symptoms of DM or visual impairment). past history (history of previous medical illness, drug intake and ocular illness and treatment)]. **Laboratory investigation included: [**Fasting blood glucose (FBG), post-prandial blood glucose (PPBG) and Glycosylated hemoglobin (HBA1c), serum urea, albumin, creatinine and measuring of albumin/ creatinine ratio, urine albumin that was measured at morning and liver function tests (SGOT, SGPT)].

Comprehensive eye examination including:

Visual acuity: Measuring of uncorrected visual acuity (UCVA) and the best corrected visual acuity (BCVA) by using Snellen's chart according to Health Resources and Services Administration.

Manifest refraction: using the autorefractometer (Topcon KR-800 Tokyo, Japan), pre- and post-dilatation with Cyclopentolate 1% eyedrops.

Slit lamp biomicroscopy: (Nidek, 22631, 2013, Nidek Japan) to examine the anterior segment of the eye to exclude any corneal or lens abnormalities as corneal opacities, corneal dystrophy, corneal degeneration or cataract.

Intraocular pressure (IOP): measurement by applanation tonometer (Keeler, UK).

Fundus examination: using slit lamp with +78D Volk lenses to exclude any posterior segment disorder. Indirect Ophthalmoscopy (+20D lens) for more details of the fundus.

Anterior chamber (AC): examination including AC depth (ACD) and trabecular meshwork.

Color Photography and Fluorescein angiography (FA): was done to all patients to differentiate cases with DR.

OCTA: Angiography–OCT OPTOVUE RTVue XR Avanti system (Opteva Inc., Fairmont, CA, USA) was done to all volunteers for investigation of retinal thickness and retinal vascular pattern according to the manufacturer's tool and analytical Angio–Vue software. We concentrated in measuring central subfield thickness (CFT), Foveal Avascular Zone (FAZ) area, retinal vessel density in a 300 –um- wide region around the FAZ (FD - 300) and Grid based vessel density (VD%) in a 9 quadrants for superficial and deep plexuses as follows: central middle (CM), central temporal (CT), central nasal (CN), upper middle (UP), upper nasal (UN), upper temporal (UT), lower middle (LM), lower nasal (LN), and lower temporal (LT). captured in 6 x 6 mm sections, automatically centered on the fovea. All the scans were performed for all patients in the same time frame from 10–12 AM to avoid possible diurnal variation.

Multifocal Electroretinogram: It was performed with RETI-scan system (Roland Consult, Electrophysiologist Diagnostic System, Brandenburg, Germany) following ISCEV (International Society for Clinical Electro-physiology of Vision) guidelines.

Approval Code: MS 44-7-2022

Statistical analysis:

Pre-coded data were processed and statistically analyzed using the statistical package of the social science software (SPSS Inc., Chicago, IL, USA), version

25, released in 2017. Data were summarized using mean & SD for quantitative variables. A normal distribution of variables was assessed using the Kolmogorov–Smirnov test. Number and Percentage were used for qualitative variables. Comparison between qualitative variables was done using the Chi-square test, while an independent t-test was used to compare quantitative variables between means. Nonparametric Kruskal-Wallis and Mann-Whitney tests were used for quantitative variables which were not normally distributed. Pearson correlation coefficient (r) was done between variables. P value of < 0.05 indicates significant results.

Cases presentation:

Case 1 (control): Male patient, 57y , BCVU : OD =0.5 , OS 0.7 .Normal IOP .No history of ocular surgeries or systemic diseases. Figure 1

Case 2 (Diabetic without retinopathy): Female patient, 50y diabetic for 11y, HbA1c=7.9, s. creatinine=1.1, No history of ocular surgeries or other systemic diseases. BCVA OD=0.3, OS=0.3. Fundus examination: myopic and no DR. Figure 2

Case 3 (DR): Female patient, 49y, Diabetic for13y, HbA1c=9.4, s. creatinine=1.0. No history of ocular surgeries or other systemic diseases. BCVA OD=0.1, OS=0.05. Figure 3

Results

Table 1 compares demographic data of studied groups, Hb A1c was significantly higher in diabetic retinopathy group. OCT measurement of thickness showed statistically significantly higher thickness in patients with retinopathy as regard to central, inner superior and outer temporal. We found a statistically significantly higher volume in DR group. OCT superficial density measurements showed statistically significant lower value in DR group as regard to Inner superior, inner inferior, inner temporal, outer superior, outer inferior, outer temporal and outer nasal. OCT deep density measurements showed statistically significant lower value in DR group as regard to inner superior, inner inferior, inner temporal, and inner nasal. Comparison of OCT angiometrics between studied groups showed only significantly higher value in Cube Avg. thickness in Diabetic retinopathy group. Study of mfERG rings showed statistically lower value of P1 response density in the no DR and DR groups compared to the control group and delayed P1 implicit time in the no DR and DR group compared to the control group.

We found a good negative correlation between mfERG and DM duration in Ring 1,2,3, 4 and 5 Resp den. And week positive correlation with Ring 3, 4 and 5 p1. implicit time. In Diabetic patients without retinopathy, we found a good positive correlation between Cub Avg. thickness and mfERG in Ring 2 Resp den. FAZ area and Ring 5 Resp den. FAZ perimeter and Ring 4 Resp den, and Ring 5 Resp den. And A good negative correlation between Cub Avg. thickness and Ring 5 p1. Implicit time, while in patients with retinopathy we found a good positive correlation with Ring 1 Resp den, Ring 5 p1. implicit time and FAZ area. Table 2

We found significant negative good correlation between Ring 5 p1. implicit time and inner superior and temporal, Ring 5 p1. Resp den and central 1mm. And a significant good positive correlation between Ring 4 p1. implicit time and inner nasal. There was a significant positive good correlation between inner superior and Ring 1 p1. Resp den, Ring 3 and 5 p1. implicit time. A significant positive good correlation between Inner inferior and Ring 2, 3 p1. implicit time. And Ring 1 p1. Resp den. A significant positive good correlation between outer nasal and Ring 2, 3 p1. implicit time. And Ring 2,3 p1. Resp den. There was a significant negative good correlation between Ring 5 p1. implicit time and all superficial density except inner temporal. There was a significant negative good correlation between Ring 5 p1. implicit time and

Central 1 mm, Inner nasal, Outer superior and Outer inferior. Table 3

Table 1: Demographic data of the studied groups

		Control		No DR		DR		P value
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age (years)		**49**	**10.3**	**53.1**	**14.6**	**55.8**	**12.9**	**0.5**
DM duration (years)		-	-	**10**	**4**	**10.5**	**6.4**	**0.001***
HbA1c		**5.4**	**0.2**	**7.2**	**1.6**	**8.6**	**0.6**	**0.001***
Intraocular pressure	**RT**	**13.6**	**1.2**	**13.3**	**1.1**	**14.1**	**0.7**	**0.2**
	LT	**13.6**	**1.7**	**13.2**	**1.2**	**14.4**	**1.17**	**0.1**
BCVA	**RT**	**0.7**	**0.4**	**0.5**	**0.4**	**0.4**	**0.2**	**0.1**
	LT	**0.7**	**0.4**	**0.5**	**0.3**	**0.5**	**0.3**	**0.3**
		N	**%**	**N**	**%**	**N**	**%**	
Sex	**Female**	**10**	**50**	**20**	**100**	**12**	**60**	**0.03***
	Male	**10**	**50**	**0**	**0**	**8**	**40**	
		OCT						
		Thickness measurement						
Central 1 mm		**250.8**	**32.9**	**247.9**	**20.5**	**318.9**	**20.9**	**0.004***
Inner superior		**312.6**	**17.4**	**314.6**	**20.7**	**341.7**	**64.3**	**0.05***
Inner inferior		**306.9**	**14.4**	**314.6**	**17.9**	**341.3**	**82.8**	**0.08**
Inner temporal		**296.5**	**21.3**	**458.8**	**70.4**	**343.5**	**73.6**	**0.4**
Inner nasal		**306.4**	**17.1**	**310.7**	**22.1**	**340.9**	**65.4**	**0.02**
Outer superior		**283.3**	**10.7**	**284.7**	**14.4**	**296.9**	**46.9**	**0.3**
Outer inferior		**269.2**	**12.7**	**277.3**	**10.9**	**284.8**	**51.2**	**0.3**
Outer temporal		**268.7**	**14.1**	**271**	**14**	**294.3**	**56.9**	**0.04***
Outer nasal		**284.9**	**21.3**	**293.9**	**15.7**	**308.5**	**54.8**	**0.1**
		Volume measurement						
Central 1 mm		**0.2**	**0.02**	**0.2**	**0.01**	**0.3**	**0.09**	**0.003***
Inner superior		**0.45**	**0.03**	**0.49**	**0.02**	**0.53**	**0.1**	**0.001***
Inner inferior		**0.46**	**0.03**	**0.49**	**0.02**	**0.53**	**0.1**	**0.02***
Inner temporal		**0.45**	**0.03**	**0.47**	**0.02**	**0.53**	**0.1**	**0.001***
Inner nasal		**0.45**	**0.03**	**0.48**	**0.02**	**0.53**	**0.1**	**0.003***
Outer superior		**0.7**	**0.2**	**0.9**	**0.04**	**0.9**	**0.1**	**0.001***
Outer inferior		**0.7**	**0.1**	**0.8**	**0.03**	**0.9**	**0.2**	**0.001***
Outer temporal		**0.6**	**0.2**	**0.8**	**0.03**	**0.9**	**0.1**	**0.001***
Outer nasal		**0.7**	**0.2**	**0.9**	**0.04**	**0.97**	**0.2**	**0.001***
		Superficial density measurement						
Central 1 mm		**0.2**	**0.07**	**0.2**	**0.08**	**0.2**	**0.07**	**0.2**
Inner superior		**0.51**	**0.05**	**0.49**	**0.08**	**0.43**	**0.09**	**0.01***
Inner inferior		**0.49**	**0.09**	**0.51**	**0.04**	**0.45**	**0.07**	**0.03***
Inner temporal		**0.5**	**0.05**	**0.49**	**0.05**	**0.44**	**0.08**	**0.009***
Inner nasal		**0.49**	**0.05**	**0.49**	**0.5**	**0.44**	**0.09**	**0.03**
Outer superior		**0.52**	**0.03**	**0.49**	**0.04**	**0.45**	**0.06**	**0.001***
Outer inferior		**0.49**	**0.04**	**0.49**	**0.03**	**0.44**	**0.06**	**0.001***
Outer temporal		**0.48**	**0.04**	**0.44**	**0.05**	**0.4**	**0.05**	**0.001***
Outer nasal		**0.54**	**0.03**	**0.52**	**0.04**	**0.46**	**0.06**	**0.001***
		Deep density measurement						
Central 1 mm		**0.39**	**0.09**	**0.32**	**0.09**	**0.37**	**0.09**	**0.1**
Inner superior		**0.56**	**0.05**	**0.57**	**0.09**	**0.5**	**0.06**	**0.01***
Inner inferior		**0.56**	**0.06**	**0.54**	**0.05**	**0.5**	**0.07**	**0.02***
Inner temporal		**0.56**	**0.06**	**0.55**	**0.06**	**0.49**	**0.09**	**0.02***
Inner nasal		**0.58**	**0.04**	**0.55**	**0.04**	**0.51**	**0.07**	**0.01***
Outer superior		**0.54**	**0.07**	**0.51**	**0.09**	**0.49**	**0.07**	**0.1**
Outer inferior		**0.49**	**0.09**	**0.49**	**0.08**	**0.48**	**0.09**	**0.8**
Outer temporal		**0.54**	**0.06**	**0.51**	**0.09**	**0.48**	**0.08**	**0.07**
Outer nasal		**0.51**	**0.09**	**0.51**	**0.09**	**0.47**	**0.08**	**0.3**
		OCT angiometrics						
Cube Avg. thickness		**6.9**	**0.2**	**7.1**	**0.3**	**7.6**	**1.3**	**0.03***
FAZ area		**0.2**	**0.07**	**0.3**	**0.1**	**0.2**	**0.1**	**0.1**
FAZ perimeter		**1.9**	**0.2**	**2.2**	**0.6**	**1.9**	**0.5**	**0.07**
		mfERG rings						
Ring 1	**p1. implicit time**	**38.7**	**7.5**	**42.5**	**4.3**	**38.9**	**11.1**	**0.3**
	Resp den	**120.9**	**57.5**	**54.4**	**22.2**	**82.3**	**19.2**	**0.03***
Ring 2	**p1. implicit time**	**40.2**	**4.6**	**40.9**	**5.4**	**41.5**	**3.7**	**0.7**
	Resp den	**48.2**	**13.2**	**26.3**	**9.5**	**27.2**	**17.5**	**0.001***
Ring 3	**p1. implicit time**	**38.9**	**2.3**	**42.4**	**1.6**	**42.4**	**4.6**	**0.001***
	Resp den	**23.5**	**5.6**	**17.5**	**5.2**	**20.4**	**14.2**	**0.1**
Ring 4	**p1. implicit time**	**39.8**	**1.03**	**40.9**	**2.5**	**40.4**	**4.3**	**0.5**
	Resp den	**16.8**	**2.2**	**11.8**	**4.4**	**14.6**	**1.8**	**0.1**
Ring 5	**p1. implicit time**	**40.2**	**1.3**	**42.5**	**2.9**	**42.2**	**3.3**	**0.02***
	Resp den	**11.5**	**1.3**	**8.8**	**2.9**	**9.1**	**3.06**	**0.003***

One way ANOVA test; Chi square test; * significant

Table 2: Correlation between mfERG ring and DM duration and correlation coefficients between OCT angiometrics and mfERG rings measures in diabetes with and without DR

	DM duration	
	r	**P value**
Ring 1p1.implicit time	0.04	0.7
Ring 1Resp den	-0.4	**0.004***
Ring 2p1.implicit time	-0.1	0.6
Ring 2Resp den	-0.5	**0.001***
Ring 3p1.implicit time	0.3	**0.05***
Ring 3Resp den	-0.3	**0.01***
Ring 4p1.implicit time	0.4	**0.008***
Ring 4Resp den	-0.3	**0.007***
Ring 5p1.implicit time	0.3	**0.03**
Ring 5Resp den	-0.5	**0.001***

Correlation between OCT angiometrics and mfERG rings measures in diabetes with and without DR

	Without DR	**Cube Avg. thickness**	**FAZ area**	**FAZ perimeter**
Ring 1	**p1. implicit time**	-0.3	-0.4	-0.4
	Resp den	-0.1	0.3	0.3
Ring 2	**p1. implicit time**	0.1	0.1	0.1
	Resp den	**0.5***	0.2	0.2
Ring 3	**p1. implicit time**	-0.3	-0.3	-0.3
	Resp den	0.4	0.2	0.2
Ring 4	**p1. implicit time**	-0.1	-0.2	-0.4
	Resp den	0.2	0.4	**0.5***
Ring 5	**p1. implicit time**	**-0.6***	-0.4	-0.30
	Resp den	0.001	**0.6***	**0.6***
	With DR	**Cube Avg. thickness**	**FAZ area**	**FAZ perimeter**
Ring 1	**p1. implicit time**	-0.2	-0.1	-0.1
	Resp den	-0.1	**0.5***	0.4
Ring 2	**p1. implicit time**	0.4	0.1	0.1
	Resp den	0.1	0.1	0.1
Ring 3	**p1. implicit time**	-0.2	0.02	-0.009
	Resp den	-0.2	0.4	0.3
Ring 4	**p1. implicit time**	0.4	-0.4	-0.3
	Resp den	-0.1	0.4	0.3
Ring 5	**p1. implicit time**	-0.1	**0.5***	0.2
	Resp den		0.2	0.2

* significant; r= Pearson correlation

Table 3: Correlation coefficients between Superficial and deep density and mfERG rings measures in diabetes with and without DR.

	Central 1 mm	Inner superior	Inner inferior	Inner temporal	Inner nasal	Outer superior	Outer inferior	Outer temporal	Outer nasal
Superficial Density and mfERG rings measures in diabetes with DR									
Ring 1p1.IT	0.2	-0.1	0.1	-0.2	0.2	0.4	-0.1	0.1	0.1
Ring 1Resp den	-0.2	-0.2	-0.2	-0.2	-0.1	-0.2	-0.2	0.1	0.0
Ring 2p1.IT	-0.1	0.4	0.0	0.2	-0.2	-0.2	-0.2	0.4	0.0
Ring 2Resp den	-0.1	0.3	0.1	0.1	0.0	-0.2	-0.1	0.3	-0.1
Ring 3p1.IT	-0.1	-0.1	0.0	-0.4	0.0	0.0	-0.4	0.1	0.0
Ring 3Resp den	-0.1	0.4	0.0	0.2	-0.1	-0.1	-0.2	0.3	-0.1
Ring 4p1.IT	0.3	-0.2	0.3	-0.2	**0.6***	0.3	0.1	0.1	0.2
Ring 4Resp den	-0.3	0.2	-0.2	0.1	-0.1	-0.2	-0.2	0.2	-0.1
Ring 5p1.IT	0.0	**-0.5***	-0.1	**-0.5***	0.1	0.2	0.0	-0.1	0.3
Ring 5Resp den	**-0.5***	0.2	-0.3	0.2	-0.3	-0.3	0.0	0.1	-0.2
Deep Density and mfERG rings measures in diabetes with DR									
Ring 1p1.IT	0.3	0.1	-0.1	-0.2	0.0	0.4	0.3	0.1	0.1
Ring 1Resp den	0.1	**.5***	**.6***	0.2	0.3	0.3	0.2	0.3	0.4
Ring 2p1.IT	-0.1	0.4	**.5***	**.5***	0.2	0.1	0.2	**.5***	**.5***
Ring 2Resp den	0.0	0.2	0.3	0.2	0.2	0.2	0.3	0.4	**.5***
Ring 3p1.IT	0.1	**.7***	**.5***	-0.1	0.0	0.4	0.3	0.3	**.6***
Ring 3Resp den	-0.2	0.1	0.3	0.3	0.2	0.2	0.3	0.4	**.5***
Ring 4p1.IT	0.3	0.2	0.0	-0.4	-0.1	0.4	0.3	0.0	0.3
Ring 4Resp den	-0.4	0.0	0.2	0.2	0.2	0.1	0.1	0.3	0.3
Ring 5p1.IT	0.3	**.6***	0.1	-0.2	-0.1	0.1	0.0	-0.1	0.0
Ring 5Resp den	-0.4	0.0	0.2	0.4	0.3	0.0	0.1	0.2	0.2
Superficial density and mfERG rings measures in diabetes without DR									
Ring 1p1.IT	-0.2	-0.3	-0.2	-0.2	0.0	0.0	0.0	-0.1	-0.2
Ring 1Resp den	-0.4	-0.1	-0.3	0.0	-0.4	-0.4	-0.3	-0.3	-0.2
Ring 2p1.IT	-0.1	0.0	-0.4	-0.1	-0.1	-0.1	0.2	-0.1	0.2
Ring 2Resp den	-0.1	0.1	-0.1	0.1	-0.2	-0.1	-0.1	0.0	0.0
Ring 3p1.IT	-0.1	-0.4	**-0.6***	-0.1	**-0.5***	-0.2	-0.1	-0.4	0.3
Ring 3Resp den	-0.3	0.1	-0.1	0.1	-0.2	-0.3	-0.2	-0.2	-0.1
Ring 4p1.IT	0.3	0.1	-0.2	0.1	0.2	0.3	.446*	0.3	0.4
Ring 4Resp den	-0.2	0.0	-0.2	0.1	-0.3	-0.2	-0.2	-0.2	0.0
Ring 5p1.IT	**-0.6***	**-0.6***	**-0.5***	-0.4	**-0.7***	**-0.7***	**-0.6***	**-0.8***	**-0.5***
Ring 5Resp den	-0.2	0.2	0.1	0.2	0.0	-0.1	0.0	0.1	-0.2
Deep Density and mfERG rings measures in diabetes without DR									
Ring 1p1.IT	0.2	0.2	0.0	0.2	0.0	0.1	0.1	0.1	0.0
Ring 1Resp den	**-0.5***	-0.1	0.0	0.0	-0.3	-0.3	-0.2	-0.2	-0.2
Ring 2p1.IT	-0.3	0.0	-0.2	-0.4	-0.3	-0.2	-0.1	-0.4	-0.1
Ring 2Resp den	-0.2	-0.1	0.0	-0.1	-0.2	-0.2	-0.2	-0.1	-0.2
Ring 3p1.IT	0.0	0.0	0.0	0.1	-0.1	0.0	0.3	0.0	0.3
Ring 3Resp den	-0.4	-0.1	0.0	0.0	-0.2	-0.2	-0.2	-0.1	-0.1
Ring 4p1.IT	0.2	0.2	0.0	0.0	0.3	0.2	0.3	0.1	0.3
Ring 4Resp den	-0.4	-0.1	0.1	0.0	-0.2	-0.2	-0.1	-0.1	-0.1
Ring 5p1.IT	**-0.7***	-0.4	-0.4	-0.2	**-0.6***	**-0.6***	**-0.5***	-0.4	-0.4
Ring 5Resp den	0.0	0.2	0.2	0.2	0.0	-0.1	0.0	0.1	-0.1

* significant; r= Pearson correlation

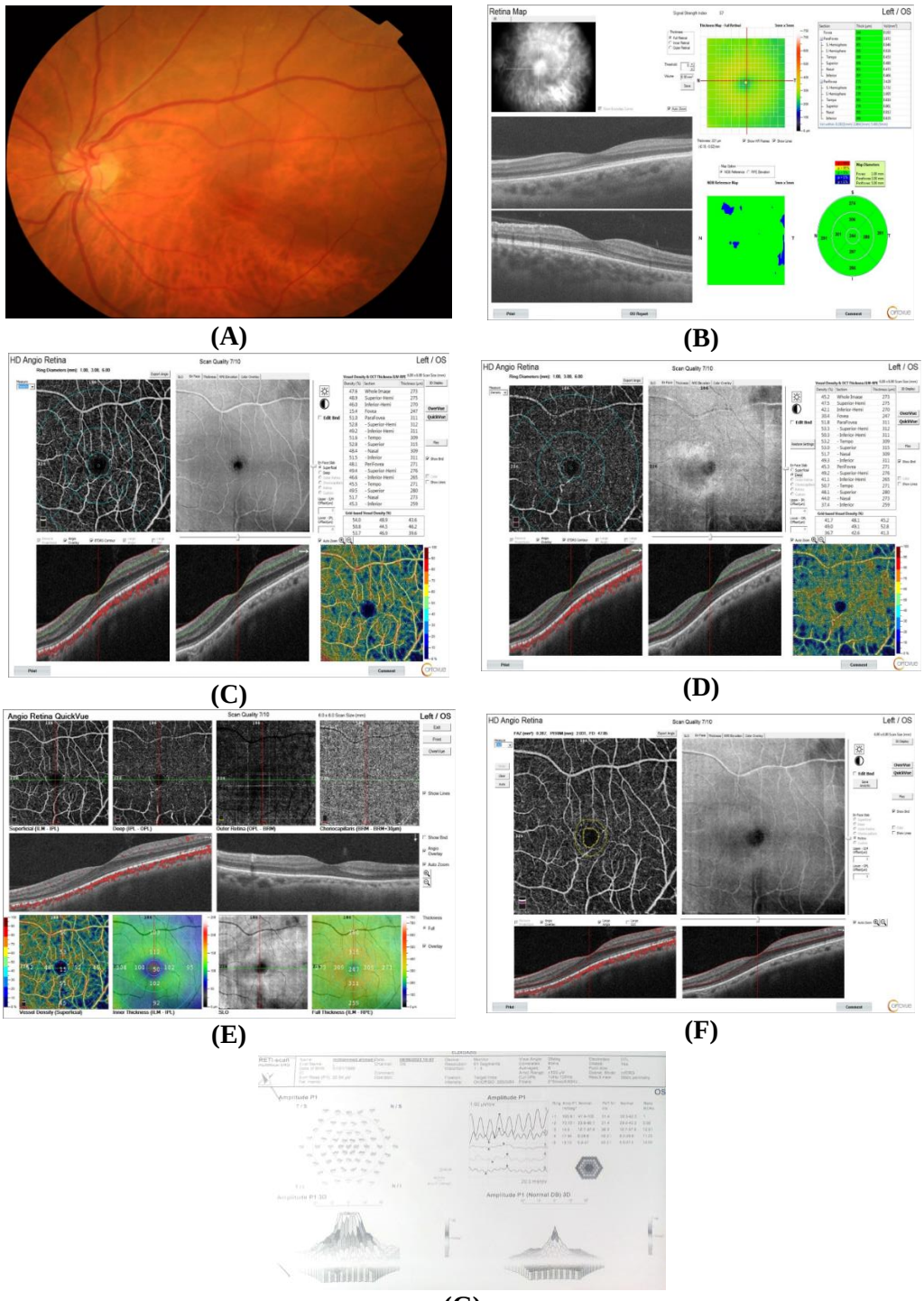

Figure 1: Case in control groups, (A) colored fundus photo of the left eye, (B) OCTA of left eye showing retinal map (CMT=244), (C) OCTA showing superficial vessel density and macular thickness, (D) OCTA showing the deep vessel density and macular thickness, (E) OCTA showing the vessel density and macular thickness, (F) OCTA of the same case showing FAZ=0.287 ,FAZ PERIM=2.031, (G) mfERG of the same case showing normal macular response

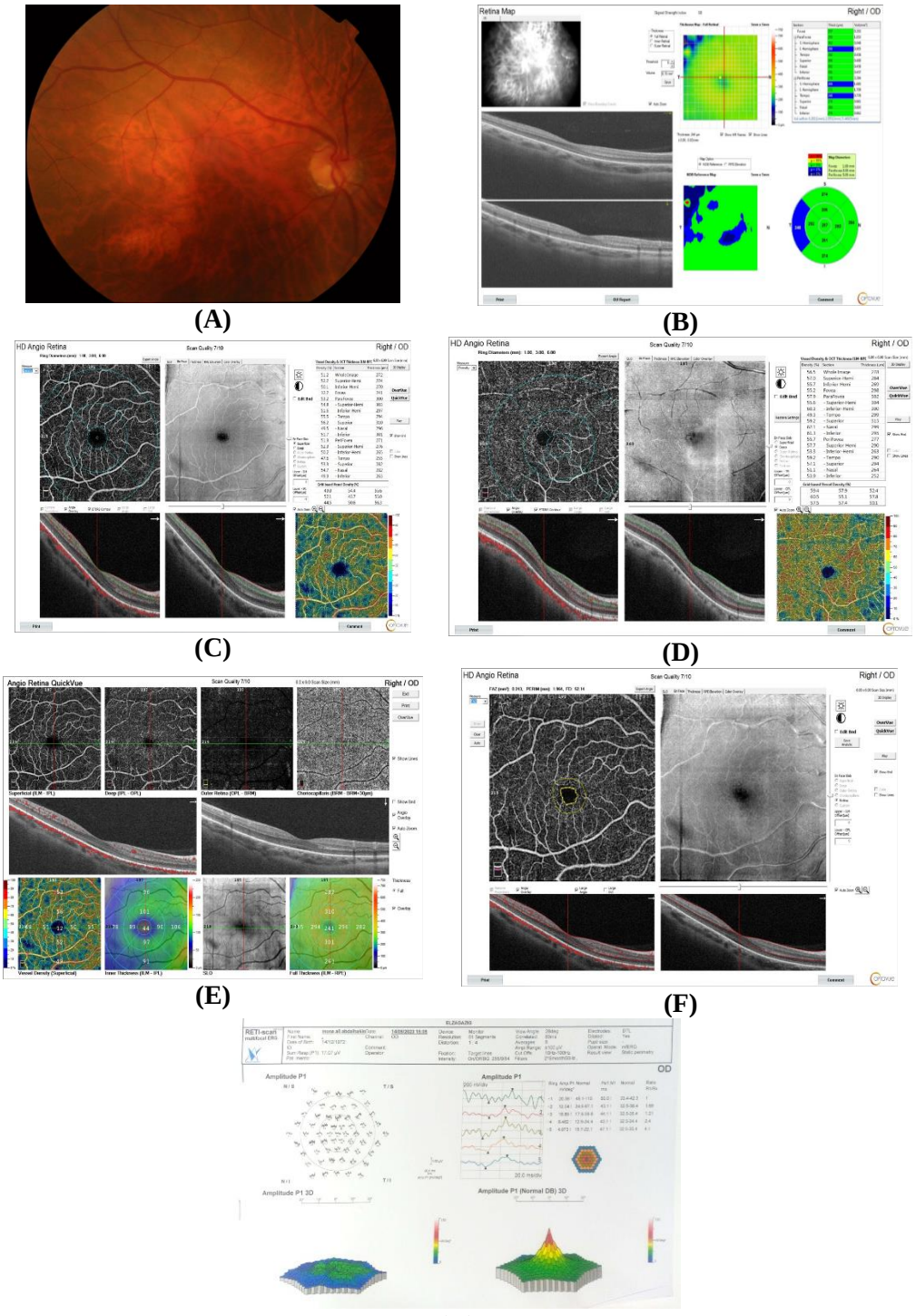

Figure 2: Case of the diabetic without retinopathy, (A) Coloured fundus photo of the right eye , (B) OCTA of right eye showing retinal map (CMT=257) . (C)OCTA showing superficial vessel density and macular thickness. (D) OCTA showing deep vessel density and macular thickness. (E) OCTA showing the vessel density and macular thickness. (F) OCTA showing FAZ=0.243 ,FAZ PERIM=1.964. (G) mfERG showing RT marked diminished macular response

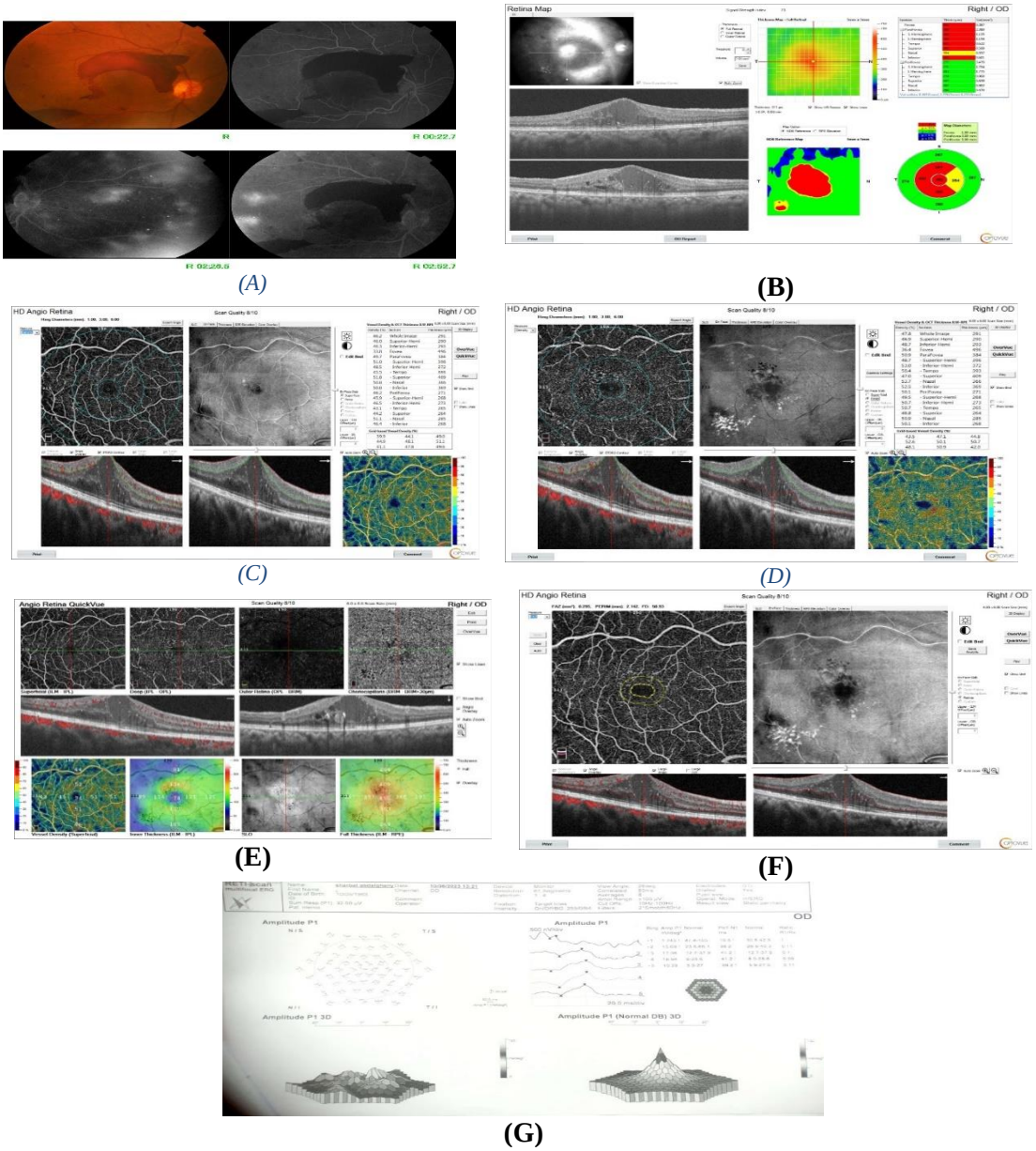

Figure 3: Case of diabetic retinopathy group, (A) Coloured fundus photo of the right eye shows macular exudates and areas of small dot hemorrhage. Fluorescein angiography shows features of proliferative diabetic retinopathy (PDR) . there are multiple hyperfluorescnce areas compatible with vascular leakage from neovascularization elsewhere (NVE) and blockage of fluorescein due to large semicircular pre retinal hemorrhage. (B) OCTA of the right eye of case (3) of diabetic retinopathy group showing retinal map (CMT=492) . (C) OCTA of the same case showing superficial vessel density and macular thickness (D) OCTA of the same case showing deep vessel density and macular thicknes (E) OCTA of the same case showing central involved macular edema (cystoid macular edema), no neovascularization within macular area . (F) OCTA of the same case showing FAZ=0.295 ,FAZ PERIM=2.142 . (G) mf ERG of the same case showing right diminished macular response.

Discussion

There is statistically significantly higher retinal thickness in patients with diabetic retinopathy as regard to central, inner superior and outer temporal quadrants than the other two groups without retinopathy measured by OCT.

In Frizziero et al. [8] study, HRF increased both in the inner and outer retina in diabetic eyes versus controls, with no differences between the diabetic groups, suggesting that local retinal inflammation occurs early, before clinically detectable retinopathy.

Comparison of retinal volume measurement showed significant increase in volume in DR group than the two other groups ($p < 0.05$) in all quadrants of the retina measured by OCT. Comparison of OCTA between studied groups showed significantly higher values in cube average thickness in DR group. OCTA superficial density measurements showed statistically significant lower value in DR group as regard to inner superior, inner inferior, inner temporal, outer superior, outer inferior, outer temporal and outer nasal quadrants of the retina. Also, OCTA deep density measurements in our study showed statistically significant lower value in DR group as regard to inner superior, inner inferior, inner temporal, and inner nasal quadrants.

A decrease in the vessel density and perfusion in the macula is reported in those with NPDR compared to those with diabetes with No DR [9]. Srinivasan et al. [10] observed that that the OCT angiometric measures did not differ in the NPDR group but demonstrated delayed implicit times in all rings when compared to the No DR group. This could likely be a sign of macular ischemia in the absence of visible signs of ischemia on OCTA.

OCTA analysis confirmed the presence of retinal vascular changes in diabetic eyes, even with mild or no DR, as previously reported [11, 12]. However, when evaluating the two diabetic groups and the three single retinal vascular plexuses separately, distinct specific changes were found. In no-DR eyes, OCTA parameters (VAD, VLF, and FD) in the SVP were significantly reduced compared to both DR eyes and controls, with no changes in the other two deeper plexuses. Onishi et al. [13] also found changes of SVP parameters on OCTA even in preclinical stages of DR and concluded that this early alteration may help to distinguish healthy from diabetic eyes.

In the current study of mfERG rings show statistically lower value of P1 response density in the no DR and DR groups compared to the control group and delayed P1 implicit time in the no DR and DR group compared to the control group. In DR patients in our study regarding superficial vessel density and mfERG measures ,We found significant negative good correlation between ring 5 p1 implicit time and inner superior and temporal, ring 5 p1 Response density and central 1mm and a significant good positive correlation between ring 4 p1 implicit time and inner nasal . In DR patients regarding deep vessel density and mfERG measures We found significant positive good correlation between inner superior and Ring 1 p1 response den, ring 3 and 5 p1 implicit time. A significant positive good correlation between inner inferior and Ring 2, 3 p1 implicit time and ring 1 p1 response density. A significant positive good correlation between outer nasal and ring 2, 3 p1 implicit time and ring 2,3 p1 response density. In Diabetic patients without retinopathy regarding superficial vessel density and mfERG measures, We found significant negative good correlation between Ring 5 p1 implicit time and all superficial density except inner temporal. Also, regarding deep density and mfERG measures ,there is significant negative good correlation between ring 5 p1 implicit time and central 1 mm, inner nasal, outer superior and outer inferior.

In agreement with our results, Srinivasan et al. [2] found that that the OCT

angiometric measures did not differ in the NPDR group compared to No DR group but the P1 implicit times in all rings were delayed and response density in rings 5 and 6 were significantly lower in those with NPDR compared to No DR. The above findings are already well established in DR. Nevertheless, data in individuals with diabetes with No DR is rare. They found that in eyes with No DR, the P1 implicit time in almost all mfERG rings are delayed in relation to lower macular vessel density and perfusion like our results.

In eyes with no DR, we observed that a lower macular vessel density and perfusion are correlated with delayed P1 implicit times and lower response densities in almost all rings.

The previously mentioned results are in coordination with Srinivasan et al. [(2)] who found minimum variance in P1 implicit times was noted as 4% and maximum variance was noted to be 7% in relation to both, vessel density and perfusion. The minimum variance in P1 response density was noted to be 7–8% and the maximum variance ranged between 11% and 13% for vessel density and perfusion, suggesting that 13% of the variance in the P1 response density is attributed to lower macular perfusion in eyes with No DR. A likely explanation for the relatively lower correlations could be that we examined only the superficial capillary plexus.

The reduced macular vessel density and/or perfusion in our study may suggest occlusion or destruction of parafoveal retinal capillaries and it also influences the retinal function assessed by mfERG in the absence of DR. The assessment shows early functional impairment even before structural alterations are clinically visible.

Similarly, a recent study by Ratra et al. [(14)] observed that OCT angiometric parameters did not show significant differences between the two groups. However, the mfERG amplitudes in rings 1–5 were reduced and the implicit times in rings 4–6 were significantly delayed in individuals with prediabetes compared to those with no diabetes. Their study demonstrated changes in the mfERG parameters before retinal structural changes are noted on OCTA indicating that these changes might start as early as the prediabetic stage. We observed that in the NPDR group, the P1 response densities in rings 2 and 3 showed a tendency to be lower in relation to lower macular perfusion but are not significant.

In our study, in diabetic patients without retinopathy, we found a good positive correlation between cub average thickness and mfERG in ring 2 response density FAZ area and ring 5 response density FAZ perimeter and ring 4 response vessel density, and ring 5 response density and a good negative correlation between cub average thickness and ring 5 p1 implicit time. While in patients with retinopathy we found a good positive correlation with Ring 1 Response den, Ring 5 p1. Implicit time and FAZ area.

Previous studies have demonstrated that the FAZ area and perimeter show an increasing trend in individuals with diabetes with DR compared to those with no diabetes and an increasing trend in various grades of NPDR [(9, 15)].

Our study shows a similar but a nonsignificant difference in angiometric measures between the two groups. In addition, in the no DR group, there were no significant correlations between implicit time and response density with the OCTA-derived area, perimeter, or circularity measures from the superficial capillary plexus rather than the deep capillary plexus.

Consistent with our research, Xia et al. [(16)] showed that the amplitude of N1 and P1 were significantly decreased and their latency were significantly increased in five ring regions of the retina in patients with CSME.

The general characteristics of our diabetic population were comparable in the no-DR and the DR groups. Therefore, our data seems to suggest the presence of different and specific morphological and functional

characteristics that may characterize the two subgroups of this diabetic population without macular edema.

Our data showed similar results to Frizziero et al. [17] who confirms the presence of different vascular and functional characteristics in patients with and without ophthalmoscopic signs of DR, showing a different involvement of retinal plexuses at OCTA in these two types of patients.

We found a good negative correlation between mfERG and DM duration in rings 1 to 5 response density and week positive correlation with ring 3, 4 and 5 p1 implicit time.

In agreement with our results, Frizziero et al. [17] found correlation between ERG parameters and the superficial vascular density has already been suggested by Kim et al. [18]. However, in that study the use of full field ERG, instead of mfERG, evaluated the electrical activity generated throughout the whole retina, whereas we studied the mfERG response, localized at the posterior pole, corresponding to the area of analysis of OCTA.

In Xia et al. [19] study, multiple stepwise regression analysis indicated P1 amplitude density in ring 2 was the only factor that correlated with the VA. Although it remains unclear that how the cellulars were impaired underlying DME, they believed that the changes of P1 wave especially P1 amplitude density in ring 2 in this study may reflect the inner retina layer damages induced by ME, which seemed to play an important role in vision loss.

Conclusion

Both OCTA and mfERG are beneficial to early detect diabetic macular changes and can detect morphological and functional retinal changes related to diabetes. The advances in OCTA can detect early vascular damage which is correlated with severity and duration of diabetes. mfERG further detect retinal inflammation and neurodegeneration of retinal layers related to diabetes. Both vascular and functional impairment assessed by OCTA and mfERG respectively and their parameters become more severe by increasing the severity and progression of diabetic retinopathy.

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To cite this article: Maha A. Elfayoumi, Yomna A. Abdallah, Marwa A. Tabl. Assessment of OCTA and Multifocal Electroretinogram in Eyes with and Without Diabetic Retinopathy. BMFJ 2025;42(3):214-227.